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# Adiposity-Related Heterogeneity in Patterns of Type 2 Diabetes Susceptibility Observed in Genome-Wide Association Data

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**OBJECTIVE**—This study examined how differences in the BMI distribution of type 2 diabetic case subjects affected genome-wide patterns of type 2 diabetes association and considered the implications for the etiological heterogeneity of type 2 diabetes.

**RESEARCH DESIGN AND METHODS**—We reanalyzed data from the Wellcome Trust Case Control Consortium genome-wide association scan (1,924 case subjects, 2,938 control subjects: 393,453 single-nucleotide polymorphisms [SNPs]) after stratifying case subjects (into “obese” and “nonobese”) according to median BMI (30.2 kg/m<sup>2</sup>). Replication of signals in which alternative case-ascertainment strategies generated marked effect size heterogeneity in type 2 diabetes association signal was sought in additional samples.

**RESULTS**—In the “obese-type 2 diabetes” scan, *FTO* variants had the strongest type 2 diabetes effect (rs8050136: relative risk [RR] 1.49 [95% CI 1.34–1.66],  $P = 1.3 \times 10^{-13}$ ), with only weak evidence for *TCF7L2* (rs7901695 RR 1.21 [1.09–1.35],  $P = 0.001$ ). This situation was reversed in the “nonobese” scan, with *FTO* association undetectable (RR 1.07 [0.97–1.19],  $P = 0.19$ ) and *TCF7L2* predominant (RR 1.53 [1.37–1.71],  $P = 1.3 \times 10^{-14}$ ). These patterns, confirmed by replication, generated strong combined evidence for between-stratum effect size heterogeneity (*FTO*:  $P_{\text{DIFF}} = 1.4 \times 10^{-7}$ ; *TCF7L2*:  $P_{\text{DIFF}} = 4.0 \times 10^{-6}$ ). Other signals displaying evidence of effect size heterogeneity in the genome-wide analyses (on chromosomes 3, 12, 15, and 18) did

not replicate. Analysis of the current list of type 2 diabetes susceptibility variants revealed nominal evidence for effect size heterogeneity for the *SLC30A8* locus alone (RR<sub>obese</sub> 1.08 [1.01–1.15]; RR<sub>nonobese</sub> 1.18 [1.10–1.27];  $P_{\text{DIFF}} = 0.04$ ).

**CONCLUSIONS**—This study demonstrates the impact of differences in case ascertainment on the power to detect and replicate genetic associations in genome-wide association studies. These data reinforce the notion that there is substantial etiological heterogeneity within type 2 diabetes. *Diabetes* 58:505–510, 2009

Over the past year, the capacity to perform large-scale high-density genome-wide association (GWA) analyses has provided the first global view of the genetic etiology of type 2 diabetes, albeit one limited to the kinds of variants (common, modest-to-large effect sizes, tagged by single-nucleotide polymorphisms [SNPs] on commercial array platforms) for which such studies are powered (1–8). These efforts have identified several novel diabetes susceptibility pathways, but also provide an opportunity to explore, in systematic fashion, questions about the etiological heterogeneity of type 2 diabetes.

One key question relates to the extent to which type 2 diabetes reflects a single monolithic condition, as opposed to a set of distinct etiologies with common phenotypic features. If the latter, the ability to identify disease subtypes differing with respect to etiology, prognosis, progression, and treatment response may enable improved clinical management. Indeed, a molecular classification of diabetes subtype is already a reality for low-frequency high-penetrance DNA variants responsible for monogenic and syndromic forms of diabetes, such as maturity-onset diabetes of the young and mitochondrial diabetes (9). These are now considered etiologically distinct from multifactorial type 2 diabetes and benefit from specific clinical and therapeutic approaches tailored to the particular molecular diagnosis (9).

One striking feature of early GWA studies for type 2 diabetes was the observation that replicated associations between variants in the *FTO* gene and type 2 diabetes predisposition were mostly restricted to one study (1,7,8). The failure of other scans (2,4–6), despite reasonable power, to detect a diabetes association signal at *FTO* became explicable once it was revealed that the primary effect of *FTO* on diabetes risk was mediated through adiposity (8). Most of the other GWA scans had, by design or circumstance, preferentially ascertained lean type 2

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diabetic case subjects (2,4–6), thereby reducing the magnitude of the case-control difference in adiposity and attenuating the *FTO* association signal with respect to diabetes.

These observations demonstrated that differences in sample ascertainment could influence the ability to detect individual signals and the landscape of susceptibility variants detected by any given GWA study. Given the key role played by replication in the evaluation of the association signals emerging from such studies, an appreciation of the genome-wide consequences of alternative case-ascertainment strategies is essential if appropriate inferences are to be made, particularly where there is evidence of substantial heterogeneity in effect size estimates between studies.

We designed the present study to address two questions. First, how might differences in type 2 diabetes case ascertainment, according to BMI, affect the patterns of association detected through GWA studies? Second, what do such differences tell us about the etiological heterogeneity of type 2 diabetes?

To answer these questions, we used GWA data (393,453 SNPs, minor allele frequency >1%; see the supplementary information in an online appendix at <http://dx.doi.org/10.2337/db08-0906>) from the type 2 diabetes arm of the Wellcome Trust Case Control Consortium (WTCCC) (1,7). Because our main aim was to evaluate the impact of alternate strategies for case ascertainment, we first divided the type 2 diabetes case subjects into two strata of equal size (“nonobese” type 2 diabetes and “obese” type 2 diabetes) using the median case BMI (30.2 kg/m<sup>2</sup>). We then performed a GWA analysis (using similar procedures as reported for the original scan [1,7]) comparing each case stratum against the full set of 2,938 control subjects (see supplementary information and Supplementary Figure S1).

The results from this BMI-stratified reanalysis of WTCCC type 2 diabetes GWA data (1,7) are displayed in Fig. 1. As anticipated, given the known effects of *FTO*, the association between *FTO* variants (e.g., rs8050136) and type 2 diabetes was detectable only in the “obese type 2 diabetes” scan ( $RR_{\text{obeseT2D}} 1.49 [1.34–1.66]$ ,  $RR_{\text{nonobeseT2D}} 1.07 [0.97–1.19]$ , between-stratum heterogeneity, by multinomial logistic regression,  $P_{\text{DIFF}} = 7.5 \times 10^{-7}$ ). In the “obese type 2 diabetes” scan, *FTO* variants ranked first to tenth in terms of effect size and association *P* value, whereas in the “nonobese type 2 diabetes” scan, the strongest association (rs8050136) ranked only 80,215th (Table 1).

To confirm these findings, we used genotypes from previously described type 2 diabetes case-control replication sample (RS) sets also of U.K. origin (1) (supplementary information). Analysis of *FTO* genotypes in these samples using the same BMI stratification procedure (see supplementary information) replicated the GWA results. In the follow-up studies alone, conducted in the RS<sub>A</sub> and RS<sub>B</sub> samples, rs8050136 generated values of ( $RR_{\text{obeseT2D}}$ ) 1.22 (1.13–1.32) and ( $RR_{\text{nonobeseT2D}}$ ) 1.05 (0.97–1.15) ( $P_{\text{DIFF}} = 0.004$ ). When GWA and RS data were combined, the RR estimates for the “obese” and “nonobese” scans were 1.30 (1.23–1.39) and 1.06 (1.00–1.14), respectively ( $P_{\text{DIFF}} = 1.4 \times 10^{-7}$ ) (Table 2).

SNPs in *TCF7L2* exhibited the reverse pattern, with variants ranked first to twelfth in the “nonobese” scan (rs7901695:  $RR_{\text{nonobeseT2D}} = 1.53 [1.37–1.71]$ ), but reaching only 385th in the “obese” scan (rs7901695:  $RR_{\text{obeseT2D}} =$

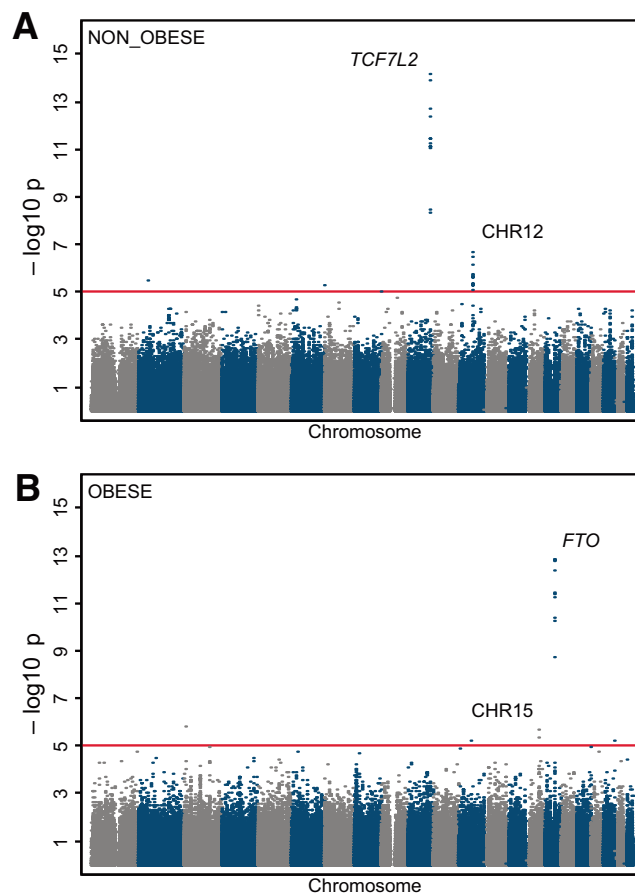


FIG. 1. Genome-wide association results for the “obese” and “nonobese” type 2 diabetes scans. A: Genome-wide type 2 diabetes association results for nonobese scan sample design. B: Genome-wide type 2 diabetes association results for obese scan sample design. The four loci labeled were those associated with type 2 diabetes in the overall scan for which stratification effects appeared most marked. (Please see <http://dx.doi.org/10.2337/db08-0906> for a high-quality digital representation of this figure.)

1.21 [1.09–1.35],  $P_{\text{DIFF}} = 0.0005$ ) (Table 1). This pattern was reproduced in the replication samples (RS<sub>A</sub> and RS<sub>B</sub>, rs7903146:  $RR_{\text{nonobeseT2D}} 1.48 [1.36–1.62]$ ,  $RR_{\text{obeseT2D}} 1.28 [1.18–1.39]$ ,  $P_{\text{DIFF}} = 0.002$ ). Between-strata heterogeneity was confirmed ( $P_{\text{DIFF}} = 4.0 \times 10^{-6}$ ) in the GWA-RS meta-analysis based on rs7903146 imputation (supplementary information and Table 2).

Inspection of GWA plots (Fig. 1) and reference to overall type 2 diabetes association effect in the WTCCC GWA analysis highlighted two other regions associated with type 2 diabetes in the overall analysis, which displayed some evidence of between-stratum heterogeneity ( $P_{\text{DIFF}} < 0.05$ ) of effect size (Table 1). Variant rs7132840 (chromosome 12) displayed a pattern similar to *TCF7L2* (i.e., predominant association in the “nonobese” scan), but the overall picture of association and heterogeneity was not confirmed within the replication samples (Supplementary Table S1). Furthermore, this SNP was not associated with type 2 diabetes in the Diabetes Genetics Initiative (DGI) and Finland–United States Investigation of NIDDM Genetics (FUSION) GWA scans, both of which featured predominantly nonobese case subjects (4,5). This SNP lies ~250 kb from a variant (rs7961581) close to the tetraspanin 8 (*TSPAN8*) gene, which has recently been shown, in a large-scale meta-analysis, to be associated with type 2 diabetes (3). However, rs7132840 and



TABLE 1  
Selected stratified type 2 diabetes association results for the WTCCC GWA

	Overall type 2 diabetes association ( <i>n</i> = 1,924/2,938)	<i>P</i> <sub>assoc</sub>	Obese type 2 diabetes versus control subjects ( <i>n</i> = 958/2,938)	<i>P</i> <sub>assoc</sub>	Nonobese type 2 diabetes versus control subjects ( <i>n</i> = 955/2,938)	<i>P</i> <sub>assoc</sub>	<i>P</i> <sub>DIFF</sub>
<i>FTO</i> (rs8050136)	1.27 (1.17–1.38)	$2.2 \times 10^{-8}$	1.49 (1.34–1.66)	$1.3 \times 10^{-13}$	1.07 (0.97–1.19)	0.19	$7.5 \times 10^{-7}$
<i>FTO</i> (rs9939609)	1.26 (1.16–1.37)	$5.6 \times 10^{-8}$	1.48 (1.33–1.64)	$3.7 \times 10^{-13}$	1.07 (0.96–1.19)	0.24	$7.7 \times 10^{-7}$
<i>TCF7L2</i> (rs7901695)	1.37 (1.26–1.49)	$8.3 \times 10^{-13}$	1.21 (1.09–1.35)	0.001	1.53 (1.37–1.71)	$1.2 \times 10^{-14}$	0.0005
<i>TCF7L2</i> * (rs7903146)	1.43 (1.31–1.56)	$4.2 \times 10^{-15}$	1.38 (1.23–1.54)	$1.4 \times 10^{-8}$	1.48 (1.33–1.66)	$4.4 \times 10^{-12}$	0.3
<i>CHR15</i> † (rs901130)	1.14 (1.06–1.22)	0.001	1.25 (1.16–1.34)	$2.0 \times 10^{-6}$	1.03 (0.91–1.13)	0.6	0.0004
<i>CHR12</i> (rs7132840)	1.20 (1.11–1.31)	$2.2 \times 10^{-8}$	1.09 (0.98–1.21)	0.096	1.32 (1.19–1.46)	$2.1 \times 10^{-7}$	0.004

The loci shown in this table included those with some evidence of type 2 diabetes association in the overall analysis ( $P < 0.001$ ) for which there was also evidence of effect size heterogeneity (Fig. 1). Median BMI = 30.2 kg/m<sup>2</sup>, *n* = number of case subjects/control subjects. RR estimates overall and by strata are generated from multinomial logistic regression. *P*<sub>assoc</sub> represents *P* value for basic type 2 diabetes association result; *P*<sub>DIFF</sub> represents a test for the difference in estimates derived from strata. \*rs7903146 imputed in the GWA data as not directly typed on the Affymetrix 500-k chip. †Data presented per copy of the major allele (as opposed to minor for others).

rs7961581 are only in weak linkage disequilibrium ( $r^2 = 0.2$ ), and rs7961581 shows no between-stratum heterogeneity of effect size (Table 3).

The other signal of interest (rs901130: chromosome 15) evokes a pattern similar to that of *FTO* (Table 1). Unlike *FTO*, this variant shows no evidence ( $P = 0.4$ ) of a primary association with BMI, based on data from a large-scale ( $n = 16,876$ ) GWA meta-analysis (10). In addition, there was no effect-size heterogeneity detectable in the replication samples ( $RS_A P_{DIFF} = 0.7$ ,  $RS_B$  not typed, Supplementary Table S1).

Next, we conducted an exploratory genome-wide analysis designed to detect additional variants that showed evidence of novel type 2 diabetes association signals only after BMI stratification (see supplementary information). Two loci demonstrated both appreciable between-stratum heterogeneity in type 2 diabetes association signal (Breslow-Day  $P < 1 \times 10^{-3}$ ) and a within-stratum type 2 diabetes association ( $P < 1 \times 10^{-3}$  in either the “obese” or “nonobese” case-control analysis) (Supplementary Figure S2).

A locus on chromosome 3 defined by the SNPs rs16827446 and rs1497313 (mutual  $r^2 = 0.2$ ) showed a predominant association in the “obese” scan (Supplementary Table S2). Although these variants showed modest associations with BMI in WTCCC case subjects ( $P = 0.004$  and  $0.003$ , respectively), these relationships were not confirmed in the control subjects ( $P = 0.5$  and  $0.1$ ), nor in the large-scale BMI meta-analysis previously mentioned ( $P > 0.2$ ) (10) and the effect was not replicated in the  $RS_A$  sample (Supplementary Table S1).

The second locus (rs917836, chromosome 18) showed evidence for a type 2 diabetes association only in the “nonobese” type 2 diabetes scan (Supplementary Table S2). However, as with rs7132840, this signal showed no evidence of a replicated type 2 diabetes association in DGI or FUSION scans, either separately (4,5) or in the recently reported meta-analysis (3), and there was no replication within  $RS_A$  (Supplementary Table S1).

Finally, we considered BMI-stratified analyses performed on 16 other confirmed type 2 diabetes susceptibility variants derived from GWA analyses, classical candidate gene studies (*KCNJ11*, *PPARG*), and pathway-based analyses (*HNF1B*, *WFS1*) (11–14) (Table 3, Supplementary Table

S3). For five of these signals (the primary signal near *CDKN2A/B* plus those in *CDKAL1*, *HHEX*, *NOTCH2*, and *SLC30A8*), there was some evidence that the association signal was more marked in nonobese case subjects, but this effect was only nominally significant for rs13266634 in *SLC30A8* ( $P_{DIFF} = 0.04$ ). As with rs7903146 in *TCF7L2*, this *SLC30A8* SNP shows evidence for an association between the risk allele and reduced BMI, which is restricted to case subjects (Supplementary Table S4).

These findings emphasize the impact that case ascertainment can have on the lead results obtained during a GWA study. The findings we report at *FTO* are in line with the expectation that variants in this gene exert their effect on type 2 diabetes susceptibility through a primary effect on adiposity. The “nonobese” scan we report here effectively matches case subjects and control subjects for BMI and, as with the DGI and French-Canadian scans (5,6), this renders *FTO* invisible to detection as a type 2 diabetes susceptibility locus.

Our findings for *TCF7L2* are also confirmatory, since the predominant action of *TCF7L2* is known to involve a deleterious effect on  $\beta$ -cell function (15). This results in a preferential association with nonobese type 2 diabetes, which likely reflects a combination of direct physiological effects (relative insulin deficiency) and ascertainment bias (most genetic studies favor relatively early-onset case subjects and may therefore oversample *TCF7L2* risk genotype case subjects who, because of marked  $\beta$ -cell deficiency, have become diabetic earlier and at lower levels of BMI than those with no *TCF7L2* risk genotypes). Associations between *TCF7L2* genotype and BMI in case subjects have been observed in several previous studies (16,17): our case data provide further evidence of these effects, while also confirming that no BMI association is evident in control subjects (Supplementary Table S4).

Apart from these regions, we found no clear examples of loci where differences in case ascertainment led to replicable effect size heterogeneity of sufficient magnitude to have masked a strong type 2 diabetes association that would have been detectable under the alternate case ascertainment strategy. However, this does not necessarily imply that *FTO* and *TCF7L2* are the only loci for which such heterogeneity of effect size could be important. Indeed, for several other now-proven type 2 diabetes

TABLE 2  
BMI-stratified analyses for *FTO* and *TCF7L2* loci in replication samples

	Obese type 2 diabetes vs. control subjects				
	RS <sub>A</sub> ( <i>n</i> = 1,718/3,596)	RS <sub>B</sub> ( <i>n</i> = 362 /1,750)	RS <sub>A</sub> + RS <sub>B</sub>	WTCCC + RS	<i>P</i> <sub>assoc</sub>
<i>FTO</i> (rs8050136)	1.20 (1.10–1.30)	1.29 (1.09–1.53)	1.22 (1.13–1.32)	1.30 (1.23–1.39)	$1.7 \times 10^{-17}$
<i>TCF7L2</i> (WTCCC imputed)	1.24 (1.13–1.36)	1.44 (1.20–1.72)	1.28 (1.18–1.39)	1.31 (1.23–1.40)	$6.1 \times 10^{-16}$
<i>TCF7L2</i> (WTCCC naive)	1.24 (1.13–1.36)	1.44 (1.20–1.72)	1.28 (1.18–1.39)	1.25 (1.17–1.34)	$1.3 \times 10^{-11}$

Stratification in the RS samples is based on the case median BMI from the WTCCC (30.2 kg/m<sup>2</sup>). Numbers in column headers refer to number of case and control subjects. RR estimates by strata are generated from multinomial logistic regression. For meanings of “imputed” and “naive” analyses, see the supplementary information. *P*<sub>assoc</sub> represents the *P* value for type 2 diabetes association derived from meta-analysis including WTCCC data; *P*<sub>DIFF</sub> represents a test for between-strata heterogeneity.

susceptibility signals, we found modest differences in effect size, consistent with the evidence that (like *TCF7L2*) their type 2 diabetes predisposition effect is mediated through reduced  $\beta$ -cell function (2,18–21). The fact that significant heterogeneity of effect size could not be detected in our analysis is most likely a reflection of power, since the modest overall effect sizes place an upper bound on the extent of between-stratum heterogeneity that could be detected in our analysis. Further work is needed to consider the effect of BMI on effect size heterogeneity in the larger type 2 diabetes GWA datasets now being generated through meta-analysis.

What are the key messages from this analysis? First, differences in case ascertainment (in this study based on BMI) can have a dramatic effect on the ranking of signals obtained from GWA scans. This can sometimes mean that even genuine signals with substantial effect sizes (such as *FTO*) fail the test of replication in additional samples (1,2,4–8). While adiposity represents one of the more obvious criteria that could be used to define case-selection strategies, it is plausible that other differences in ascertainment scheme (for example, with respect to age of

onset or family history) could also generate appreciable effect size heterogeneity. Even modest differences in effect size (too small to be easily detected in the kinds of analyses we have performed) could have a substantial impact on the power to detect signals by replication.

Second, awareness of the potential for effect size heterogeneity consequent on case ascertainment strategies can not only “rescue” genuine associations that might otherwise have been dismissed because of apparent failure to replicate, but also provides insight into the mechanisms through which the associated variants act. This phenomenon, which we have termed “informative heterogeneity,” requires, of course, that the factor explaining the heterogeneity can be identified. In the case of *FTO*, the observation that effect size heterogeneity reflected differences in case-control matching for BMI provided the clue that these variants had a primary effect on adiposity (8).

Third, these studies provide a genetic counterpart to the expectation from physiological first principles that defects in  $\beta$ -cell function would predominate in the pathogenesis of “nonobese” as opposed to “obese” type 2 diabetes. On their own, our findings do not provide justification for

TABLE 3  
BMI-stratified analyses for other confirmed type 2 diabetes susceptibility loci in GWA and RS samples

	Obese type 2 diabetes vs. control subjects				
	Obese type 2 diabetes	Obese type 2 diabetes	RS <sub>A</sub> + RS <sub>B</sub>	WTCCC + RS	<i>P</i> <sub>assoc</sub>
	RS <sub>A</sub> ( <i>n</i> = 1,718 /3,596)	RS <sub>B</sub> ( <i>n</i> = 362 /1,750)			
rs10811661 ( <i>CDKN2B</i> )	1.17 (1.04–1.31)	0.98 (0.79–1.22)	1.12 (1.01–1.24)	1.13 (1.05–1.24)	0.002
rs10946398 ( <i>CDKAL</i> )	1.12 (1.03, 1.23)	1.18 (1.00, 1.40)	1.13 (1.05–1.23)	1.14 (1.07–1.21)	0.00004
rs5015480* ( <i>HHEX</i> )	1.01 (0.93–1.10)	1.15 (0.97–1.35)	1.04 (0.96–1.12)	1.10 (1.03–1.17)	0.003
rs13266634† ( <i>SLC30A8</i> )	1.08 (0.99–1.18)	1.15 (1.00–1.39)	1.10 (1.01–1.19)	1.08 (1.01–1.15)	0.03
rs4402960 ( <i>IGF2BP2</i> )	1.10 (1.00–1.20)	0.98 (0.82–1.17)	1.07 (0.99–1.16)	1.12 (1.05–1.19)	0.0008
rs564398 ( <i>CDKN2B</i> )	1.17 (1.07–1.28)	1.03 (0.87–1.22)	1.14 (1.05–1.22)	1.15 (1.08–1.22)	0.00001
rs2934381 ( <i>NOTCH2</i> )	1.08 (0.94–1.23)	0.99 (0.76–1.28)	1.06 (0.944–1.19)	1.08 (0.98–1.18)	0.1
rs7578597‡ ( <i>THADA</i> )	1.07 (0.93–1.24)	1.23 (0.93–1.62)	1.11 (0.97–1.26)	1.14 (1.27–1.02)	0.02
rs4607103 ( <i>ADAMTS9</i> )	1.04 (0.94–1.15)	1.13 (0.93–1.37)	1.06 (0.97–1.16)	1.10 (1.02–1.18)	0.02
rs864745 ( <i>JAZF1</i> )	1.04 (0.96–1.13)	1.40 (1.18–1.65)	1.10 (1.02–1.19)	1.12 (1.05–1.19)	0.0003
rs12779790‡ ( <i>CDC123/CAMK1D</i> )	1.11 (0.99–1.23)	1.29 (1.05–1.58)	1.14 (1.04–1.25)	1.15 (1.06–1.24)	0.0005
rs7961581 ( <i>TSPAN/LGR5</i> )	1.12 (1.02–1.23)	0.99 (0.83–1.18)	1.09 (1.00–1.18)	1.13 (1.06–1.21)	0.0002
rs757210 ( <i>HNF1B</i> )	1.03 (0.95–1.13)	1.02 (0.86–1.21)	1.03 (0.96–1.11)	1.04 (0.97–1.11)	0.3
rs10010131 ( <i>WFS1</i> )	1.04 (0.96–1.12)	1.05 (0.88–1.20)	1.04 (0.97–1.11)	1.05 (0.99–1.11)	0.1
rs1801282 ( <i>PPARG</i> )	1.15 (1.03–1.25)	1.43 (1.04–1.66)	1.17 (1.06–1.26)	1.19 (1.10–1.26)	0.00004
rs5219 ( <i>KCNJ11</i> )	1.21 (1.11–1.32)	1.02 (0.86–1.22)	1.25 (1.15–1.36)	1.19 (1.11–1.27)	$5.2 \times 10^{-7}$

Stratification in the RS samples is based on the case median BMI from the WTCCC (30.2 kg/m<sup>2</sup>). Numbers in column headers refer to number of case subjects and control subjects overall. RR estimates by strata are generated from multinomial logistic regression. *P*<sub>assoc</sub> represents *P* value for type 2 diabetes association derived from meta-analysis including WTCCC data; *P*<sub>DIFF</sub> represents a test for between-strata heterogeneity. \*Meta-analysis only based on rs5015480 and the perfect proxy rs1111875 in RS<sub>A</sub> and RS<sub>B</sub>. †rs13266634 (*SLC30A8*) was not well captured by the Affymetrix chip, so WTCCC data are derived from bespoke genotyping. ‡Imputed genotype data. The *CDKN2B* locus is represented by two SNPs given evidence of two independent signals in this region (1). Detailed WTCCC results are presented in Supplementary Table S2.

TABLE 2  
Continued

Nonobese type 2 diabetes vs. control subjects					
RS <sub>A</sub> ( <i>n</i> = 1,407/3,596)	RS <sub>B</sub> ( <i>n</i> = 270 /1,750)	RS <sub>A</sub> + RS <sub>B</sub>	WTCCC + RS	<i>P</i> <sub>assoc</sub>	<i>P</i> <sub>diff</sub>
1.06 (1.96–1.16)	1.07 (0.88–1.29)	1.05 (0.97–1.15)	1.06 (1.00–1.14)	0.06	$1.4 \times 10^{-7}$
1.50 (1.36–1.65)	1.45 (1.19–1.77)	1.48 (1.36–1.62)	1.49 (1.39–1.59)	$9.1 \times 10^{-30}$	0.002
1.50 (1.36–1.65)	1.45 (1.19–1.77)	1.48 (1.36–1.62)	1.51 (1.41–1.61)	$2.9 \times 10^{-32}$	$4.0 \times 10^{-6}$

considering these as distinct phenotypes, as opposed to extremes on an etiological continuum. However, our findings do suggest that, as additional variants affecting type 2 diabetes susceptibility are defined, genetic data could complement physiological studies in defining patient subgroups that differ substantially from a pathogenetic perspective and may therefore benefit from different preventative and therapeutic approaches.

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TABLE 3  
Continued

Nonobese type 2 diabetes vs. control subjects					
Nonobese type 2 diabetes	Nonobese type 2 diabetes	RS <sub>A</sub> + RS <sub>B</sub>	WTCCC + RS	<i>P</i> <sub>assoc</sub>	<i>P</i> <sub>diff</sub>
RS <sub>A</sub> ( <i>n</i> = 1,407 /3,596)	RS <sub>B</sub> ( <i>n</i> = 270/1,750)				
1.25 (1.10–1.42)	1.28 (0.97–1.68)	1.25 (1.12–1.41)	1.26 (1.15–1.38)	$7.0 \times 10^{-7}$	0.09
1.11 (1.01–1.22)	1.29 (1.06–1.56)	1.14 (1.05–1.24)	1.18 (1.11–1.26)	$7.2 \times 10^{-7}$	0.4
1.10 (1.01–1.21)	1.21 (1.00–1.46)	1.13 (1.03–1.22)	1.16 (1.08–1.24)	0.00002	0.2
1.16 (1.06–1.28)	1.19 (0.96–1.47)	1.17 (1.07–1.28)	1.18 (1.10–1.27)	$7.1 \times 10^{-6}$	0.04
1.10 (1.00–1.21)	1.12 (0.92–1.36)	1.11 (1.01–1.20)	1.10 (1.03–1.18)	0.005	0.7
1.10 (1.00–1.21)	1.07 (0.89–1.29)	1.09 (1.01–1.19)	1.12 (1.05–1.20)	0.0006	0.5
1.14 (1.00–1.31)	1.05 (0.78–1.40)	1.12 (0.99–1.27)	1.12 (1.02–1.23)	0.02	0.5
1.12 (0.96–1.31)	1.13 (0.83–1.54)	1.12 (1.05–1.20)	1.13 (1.06–1.20)	0.0002	0.5
1.06 (0.96–1.18)	1.05 (0.85–1.31)	1.01 (0.96–1.17)	1.09 (1.01–1.17)	0.04	0.9
1.02 (0.93–1.12)	1.03 (0.85–1.24)	1.02 (0.94–1.11)	1.08 (1.01–1.15)	0.02	0.6
1.10 (0.99–1.24)	1.20 (0.95–1.51)	1.12 (1.01–1.24)	1.14 (1.05–1.23)	0.002	0.9
1.06 (0.96–1.17)	1.16 (0.95–1.41)	1.07 (0.99–1.16)	1.13 (1.06–1.20)	0.0003	0.9
1.05 (0.96–1.15)	1.13 (0.94–1.37)	1.07 (0.98–1.16)	1.07 (1.00–1.15)	0.06	0.5
1.12 (1.04–1.20)	1.14 (0.96–1.29)	1.12 (1.05–1.19)	1.13 (1.06–1.18)	0.0001	0.05
1.10 (0.97–1.21)	1.19 (0.62–1.53)	1.11 (0.98–1.21)	1.13 (1.04–1.22)	0.006	0.3
1.20 (1.10–1.32)	1.11 (0.91–1.36)	1.23 (1.13–1.35)	1.25 (1.16–1.34)	$1.3 \times 10^{-9}$	0.2

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